IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PFIZER INC. and UCB PHARMA GMBH, Plaintiffs, v. SANDOZ INC., *et al.*, Defendants.	C.A. No. 13-1110-GMS **CONSOLIDATED**

MEMORANDUM

I. INTRODUCTION

In this consolidated patent infringement action, Pfizer Inc. and UCB Pharma GmbH (collectively, "the Plaintiffs") allege that Accord Healthcare Inc., USA, Amerigen Pharmaceuticals Ltd., Amerigen Pharmaceuticals, Inc., Amneal Pharmaceuticals, LLC, and Sandoz Inc. (collectively, "the Defendants") infringe the asserted claims of the patents-in-suit. The court held a four-day bench trial in this matter on July 13 through July 16, 2015. Presently before the court are the parties' post-trial proposed findings of fact and conclusions of law concerning the validity of the patents-in-suit, specifically whether the asserted claims are invalid as obvious under 35 U.S.C. § 103. (D.I. 292; D.I. 297.)

Pursuant to Federal Rule of Civil Procedure 52(a), having considered the entire record in this case and the applicable law, the court concludes that none asserted claims of the patents-in-suit are invalid due to obviousness. These findings of fact and conclusions of law are set forth in further detail below.

II. FINDINGS OF FACT[1]

A. The Parties

1. Plaintiff Pfizer Inc. ("Pfizer") is a corporation organized and existing under the laws of Delaware and has a place of business at 235 East 42nd Street, New York, New York.

2. Plaintiff UCB Pharma GmbH is an entity organized and existing under the laws of Germany, and has a place of business at Alfred-Nobel-Strasse 10, Monheim, Germany.

3. Defendant Accord Healthcare Inc., USA ("Accord") is a company organized and existing under the laws of North Carolina and has a principal place of business at 1009 Slater Road, Suite 210-B, Durham, North Carolina.

4. Defendant Amerigen Pharmaceuticals Ltd. is a corporation organized and existing under the laws of the Cayman Islands and has a registered office at C/O Codan Trust Company (Cayman) Limited, Cricket Square, Hutchins Drive, P.O. Box 2681, Grand Cayman, KY1-1111 Cayman.

5. Defendant Amerigen Pharmaceuticals, Inc. is a company organized and existing under the laws of Delaware and has a principal place of business at 9 Polito Ave., Suite 900, Lyndhurst, New Jersey. Amerigen Pharmaceuticals, Inc. is the U.S. agent for Amerigen Pharmaceuticals Ltd (collectively, "Amerigen").

6. Defendant Amneal Pharmaceuticals, LLC ("Amneal") is a company organized and existing under the laws of Delaware and has a principal place of business at 440 US Highway 22 East, Suite 104, Bridgewater, New Jersey.

7. Defendant Sandoz Inc. ("Sandoz") is a company organized and existing under the laws of Colorado and has a place of business at 100 College Road West, Princeton, New Jersey.

8. The court has subject matter jurisdiction and personal jurisdiction over all parties.

B. Background

9. Pfizer holds approved New Drug Application ("NDA") No. 02-2030 for fesoterodine fumarate extended-release tablets, in 4 and 8 mg dosage strengths, which Pfizer sells under the trade name Toviaz®.

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[1] Prior to trial, the parties submitted an exhibit of uncontested facts in conjunction with their Pretrial Order. (D.I. 256, Ex. 1.) The court takes most of its findings of fact from the parties' uncontested facts. The court has also reordered and renumbered some paragraphs and made minor edits for the purpose of concision and clarity that it does not believe alters the meaning of the paragraphs from the Pretrial Order. Otherwise, any differences between this section and the parties' statement of uncontested facts are unintentional.

The court's findings of fact with respect to matters that were the subject of dispute between the parties are included in Part III this opinion ("Discussion and Conclusions of Law"), preceded by the phrase "the court finds" or "the court concludes."

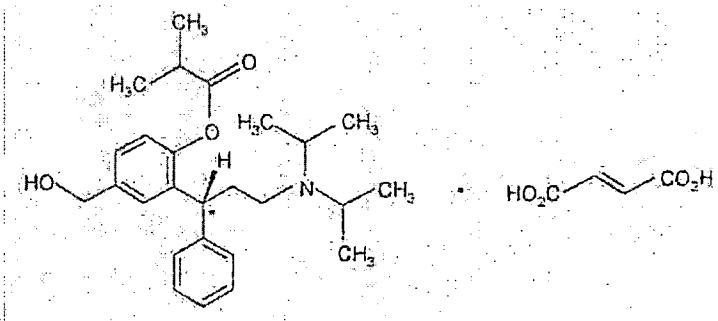
10. Toviaz® is a FDA-approved treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency. The FDA first approved the NDA for Toviaz® on October 31, 2008.

11. Pursuant to 21 U.S.C. § 335(b)(1) and attendant FDA regulations, U.S. Patent Nos. 7,384,980 ("the '980 patent"), 7,855,230 ("the '230 patent"), 7,985,772 ("the '772 patent"), 8,338,478 ("the '478 patent"), and 6,858,650 ("the '650 patent") are among the patents listed in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book") with respect to Toviaz®.

12. Fesoterodine fumarate is the active pharmaceutical ingredient in Toviaz®.

13. Chemical names for fesoterodine fumarate include:
   a. isobutyric acid 2-((R)-3-diisopropylammonium-1-phenylpropyl)-4-hydroxymethylphenyl ester hydrogen fumarate;
   b. R-(+)-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenylisobutyrate ester hydrogen fumarate;
   c. R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester hydrogen fumarate;
   d. R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester hydrogen fumarate; and
   e. R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester hydrogen fumarate.

14. The structural formula of fesoterodine fumarate is:



The asterisk (*) indicates the chiral carbon.

C. The Patents-in-Suit

15. Collectively, the '980, '230, '772, and '478 patents may be referred to as the "Compound Patents."

16. The Compound Patents each issued from common parent applications, each of which ultimately claim priority to European Application No. 98108608.5, filed May 12, 1998.

17. The '980 patent issued on June 10, 2008 and is entitled "Derivatives of 3,3-Diphenylpropylamines." The '980 patent names Claus Meese and Bengt Sparf as inventors.

18. The '230 patent issued on December 21, 2010 and is entitled "Derivatives of 3,3-Diphenylpropylamines." The '230 patent names Claus Meese and Bengt Sparf as inventors.

19. The '772 patent issued on July 26, 2011 and is entitled "Derivatives of 3,3-Diphenylpropylamines." The '772 patent names Claus Meese and Bengt Sparf as inventors.

20. The '478 patent issued on December 25, 2012 and is entitled "Derivatives of 3,3-Diphenylpropylamines." The '478 patent names Claus Meese and Bengt Sparf as inventors.

21. The '650 patent issued on February 22, 2005 and is entitled "Stable Salts of Novel Derivatives of 3,3-Diphenylpropylamines." The parties refer to the '650 patent as the "Salt Patent." It claims priority to German Patent Application No. DE 199 55 190 filed November 16, 1999. The '650 patent names Claus Meese as the inventor.

(1) <u>The Asserted Claims</u>

22. The Plaintiffs have asserted infringement of claims 1, 2, 3 and 7 of the '980 patent against each defendant.

23. The Plaintiffs have asserted infringement of claims 3 and 5 of the '230 patent against each defendant.

24. The Plaintiffs have asserted infringement of claim 3 of the '772 patent against each defendant.

25. The Plaintiffs have asserted infringement of claim 3 of the '478 patent against each defendant.

26. The Plaintiffs have asserted infringement of claims 3, 5, 23 and 24 of the '650 patent against each defendant.

i. *'980 Patent, Claim 1*

27. Claim 1 of the '980 patent claims: R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester.

ii. *'980 Patent, Claim 2*

28. Claim 2 of the '980 patent claims: A salt of R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenyl propyl)-4-hydroxymethylphenyl ester with a physiologically acceptable acid.

iii. *'980 Patent, Claim 3*

29. Claim 3 of the '980 patent claims: A pharmaceutical composition comprising an effective amount of R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl

ester, or a salt thereof with a physiologically acceptable acid and a pharmaceutically acceptable carrier.

iv. *'980 Patent, Claim 7*

30. Claim 7 of the '980 patent claims: The method according to claim 6 [*a method according to claim 5 {a method of treating a disease in a mammal that is amenable to treatment by antagonizing muscarinic receptors in the mammal, the method comprising administering to the mammal a pharmaceutical composition comprising an effective amount of R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester or a salt thereof with a physiologically acceptable acid} wherein the disease is urinary incontinence*] wherein the mammal is a human.

v. *'230 Patent, Claim 3*

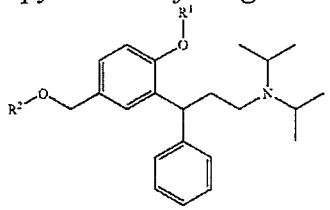
31. Claim 3 of the '230 patent claims: The method according to claim 1 [*a method of treating urinary incontinence in a patient in need thereof, the method comprising administering to the patient an effective amount of a compound selected from the group consisting of: n-butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, and acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, including the racemic mixtures and individual enantiomers of said compounds, and a salt of said compounds with a physiologically acceptable acid*], wherein the compound is R-(+) isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester.

vi. *'230 Patent, Claim 5*

32. Claim 5 of the '230 patent claims: The method according to any one of claims 1–4, wherein the compound is administered to the patient in the form of a pharmaceutical composition comprising a pharmaceutically acceptable carrier.

vii. *'772 Patent, Claim 3*

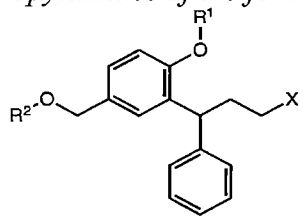
33. Claim 3 of the '772 patent claims: The 3,3-Diphenylpropylamine of claim 1 [*3,3-Diphenylpropylamines of the general formula:*



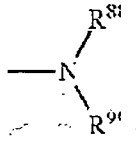
wherein R1 is hydrogen and R2 is C1-C6 alkylcarbonyl; or R1 is C1-C6 alkylcarbonyl and R2 is hydrogen; their salts with physiologically acceptable acids, their free bases and, when the 3,3-Diphenylpropylamines are in the form of optical isomers, the racemic mixture and the individual enantiomers] wherein R1 is C1-C6 alkylcarbonyl and R2 is hydrogen.

viii. *'478 Patent, Claim 3*

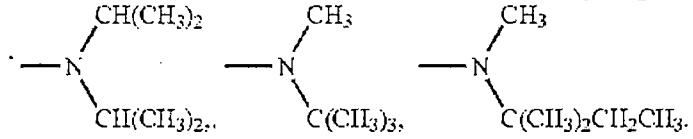
34. Claim 3 of the '478 patent claims: The 3,3-Diphenylpropylamines of claim 1 [*3,3-Diphenylpropylamines of the formula*



where: R1 is hydrogen and R2 is C1-C6 alkylcarbonyl; or R1 is C1-C6 alkylcarbonyl and R2 is hydrogen; and X is a tertiary amino group of formula

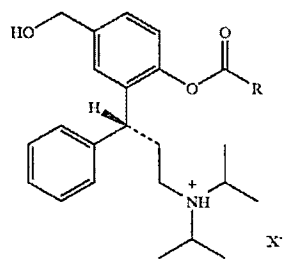


where R8 and R9 are each independently C1-C8 alkyl and together comprise at least three carbon atoms; their salts with physiologically acceptable acids, their free bases and, when the 3,3-Diphenylpropylamines are in the form of optical isomers, the racemic mixture and the individual enantiomers], where X is selected from the group consisting of:



ix. *'650 Patent, Claim 3*

35. Claim 3 of the '650 patent claims: "Compounds in accordance with claim 1, characterized in that they have general formula 2



in which R denotes C1-C6-alkyl, C3-C10-cycloalkyl, substituted or unsubstituted phenyl and X- is the acid residue of a physiologically compatible inorganic or organic acid.

x. *'650 Patent, Claim 5*

36. Claim 5 of the '650 patent claims: Compounds in accordance with claim 3, characterized in that they are R-(+)-2-(3-(diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester hydrogen fumarate, R-(+)-2-(3-(diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester-hydrochloride hydrate.

xi. *'650 Patent, Claim 23*

37. Claim 23 of the '650 patent claims: A method of treating a patient suffering from urinary incontinence, which method comprises the step of administering to said patient an effective amount of a compound according to claim 5.

xii. *'650 Patent, Claim 24*

38. Claim 24 of the '650 patent claims: The method of any one of claims 21–23, wherein the urinary incontinence disorder is urge incontinence.

(2) The Accused Products

i. *ANDA No. 205012 Submitted by Accord*

39. Accord submitted Abbreviated New Drug Application ("ANDA") No. 205012 to the FDA pursuant to 21 U.S.C. §§ 355(j), seeking approval to market fesoterodine fumarate extended-release tablets in 4 and 8 mg dosage strengths ("Accord's Product")

40. Accord's ANDA refers to and relies upon the Toviaz® NDA and contains data that, according to Accord, demonstrates that Accord's Product is bioequivalent to Toviaz®.

41. Accord included certifications in its ANDA, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), that the '650, '980, '230, '772, and '478 patents are invalid, unenforceable, or will not be infringed by the commercial manufacture, use, or sale of Accord's Product.

42. On June 7, 2013, Accord sent Notice of its Paragraph IV certifications to the Plaintiffs, providing its asserted factual and legal bases for its contentions that the '650, '980, '230, '772, and '478 patents are not infringed, invalid or unenforceable.

43. In response to Accord's Notice, on August 21, 2013, the Plaintiffs sued Accord for infringement of the '650, '980, '230, '772, and '478 patents, pursuant to 35 U.S.C. § 271(e)(2)(A).

ii. *ANDA No. 204504 Submitted by Amerigen*

44. Amerigen submitted ANDA No. 204504 to the FDA, pursuant to 21 U.S.C. §§ 355(j), seeking approval to market fesoterodine fumarate extended-release tablets in 4 and 8 mg dosage strengths ("Amerigen's Product").

45. Amerigen's ANDA refers to and relies upon the Toviaz® NDA and contains data that, according to Amerigen, demonstrates that Amerigen's Product is bioequivalent to Toviaz®.

46. Amerigen included certifications in its ANDA, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), that the '650, '980, '230, '772, and '478 patents are invalid, unenforceable, or will not be infringed by the commercial manufacture, use, or sale of Amerigen's Product.

47. On May 31, 2013, Amerigen sent Notice of its Paragraph IV certifications to the Plaintiffs, providing its asserted factual and legal bases for its contentions that the '650, '980, '230, '772, and '478 patents are not infringed, invalid or unenforceable.

48. In response to Amerigen's Notice, on June 28, 2013, the Plaintiffs sued Amerigen for infringement of the '650, '980, '230, '772, and '478 patents, pursuant to 35 U.S.C. § 271(e)(2)(A).

iii. *ANDA No. 205002 Submitted by Amneal*

49. Amneal submitted ANDA No. 205002 to the FDA, pursuant to 21 U.S.C. §§ 355(j), seeking approval to market fesoterodine fumarate extended-release tablets in 4 and 8 mg dosage strengths ("Amneal's Product").

50. Amneal's ANDA refers to and relies upon the Toviaz® NDA and contains data that, according to Amneal, demonstrates that Amneal's Product is bioequivalent to Toviaz®.

51. Amneal included certifications in its ANDA, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), that the '650, '980, '230, '772, and '478 patents are invalid, unenforceable, or will not be infringed by the commercial manufacture, use, or sale of Amneal's Product.

52. On May 24, 2013, Amneal sent Notice of its Paragraph IV certifications to the Plaintiffs, providing its asserted factual and legal bases for its contentions that the '650, '980, '230, '772, and '478 patents are not infringed, invalid or unenforceable.

53. In response to Amneal's Notice, on June 28, 2013, the Plaintiffs sued Amneal for infringement of the '650, '980, '230, '772, and '478 patents, pursuant to 35 U.S.C. § 271(e)(2)(A).

iv. *ANDA No. 204844 Submitted by Sandoz*

54. Sandoz submitted ANDA No. 204844 to the FDA, pursuant to 21 U.S.C. §§ 355(j), seeking approval to engage in the commercial manufacture, use, sale, offers for sale and importation of fesoterodine fumarate extended-release tablets in 4 and 8 mg dosage strengths ("Sandoz's Product").

55. Sandoz's ANDA refers to and relies upon the Toviaz® NDA and contains data that, according to Sandoz, demonstrates that Sandoz's Product is bioequivalent to Toviaz®.

56. Sandoz included certifications in its ANDA, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), that the '650, '980, '230, '772, '478, '715, '398, and '723 patents are invalid, unenforceable, or will not be infringed by the commercial manufacture, use, offer for sale, sale or importation of Sandoz's Product.

57. On May 9, 2013 and September 19, 2013, Sandoz sent Notices of its Paragraph IV certifications to the Plaintiffs, providing its asserted factual and legal bases for its contentions that the '650, '980, '230, '772, '478, '715, '398, and '723 patents are not infringed, invalid or unenforceable.

58. In response to Sandoz's Notice, on June 21, 2013, the Plaintiffs sued Alkem for infringement of the ''650, '980, '230, '772, and '478 patents, pursuant to 35 U.S.C. § 271(e)(2)(A).

59. Sandoz answered the complaint on August 14, 2013, denying infringement, raising affirmative defenses of invalidity, no direct infringement, no inducement of infringement, and no contributory infringement. At that time, Sandoz asserted counterclaims seeking declaratory judgment of invalidity and non-infringement of the '650, '980, '230, '772, and '478 patents, as well as the '715 and '398 patents.

D. Procedural History

60. The Plaintiffs' patent infringement claims against Accord, Amerigen, Amneal, and Sandoz were consolidated under Civil Action No. 13-1110 on November 6, 2013.

61. The court held a bench trial on July 13 through July 16, 2015. The Defendants argued that all asserted claims are invalid as obvious under 35 U.S.C. § 103. The Defendants also argued that claims 5, 23, and 24 of the '650 patent are invalid as anticipated under 35 U.S.C. § 102, and that claim 5 of the '650 patent is invalid as indefinite under 35 U.S.C. § 112(b). All defendants except for Sandoz stipulated to infringement of all asserted claims. Sandoz denied that it infringed claim 1 of the '980 patent and claim 3 of the '230 patent.

62. At the close of the Plaintiffs' production of evidence concerning infringement, Sandoz and the Plaintiffs moved pursuant to Federal Rule of Civil Procedure 52(c) for judgment on partial findings on the issue of infringement. (D.I. 272; D.I. 273.) The court ruled in favor of the Plaintiffs, finding that to the extent that the asserted claims are valid, Sandoz infringes the claims. (D.I. 276.)

63. At the close of the Defendants' prima facie case for invalidity of the asserted patents, the Plaintiffs moved pursuant to Federal Rule of Civil Procedure 52(c) for judgment on partial findings on the issues of obviousness, anticipation, and indefiniteness. (Tr. at 452:4–457:20.) The court denied the Plaintiff's motion on obviousness (Tr. at 457:23–25), and granted the Plaintiffs' motion on anticipation (Tr. at 660:16–662:25) and indefiniteness (D.I. 278).

III. DISCUSSION AND CONCLUSIONS OF LAW

The court has subject matter jurisdiction over this matter pursuant to 28 U.S.C. §§ 1331, 1338, and 2201. Venue is proper in this court under 28 U.S.C. §§ 1391 and 1400(b). The only remaining issue is whether the asserted claims of the patents-in-suit are invalid due to obviousness. The Defendants challenge the validity of each of the asserted claims, arguing that they are obvious in light of the prior art. The court finds that, for the reasons that follow, the Defendants have failed to establish by clear and convincing evidence that the patents-in-suit are obvious.

A. The Legal Standard

35 U.S.C. § 103(a) provides that a patent may not be obtained "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious to a person having ordinary skill in the art." 35 U.S.C. § 103(a). Obviousness is a question of law that is predicated on several factual inquires. *See Richardson-Vicks v. Upjohn Co.*, 122 F.3d 1476, 1479 (Fed. Cir. 1997). The trier of fact is directed to assess four considerations: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed subject matter and the prior art; and (4) secondary considerations of non-obviousness, such as commercial success, long felt but unsolved need, failure of others, acquiescence of others in the industry that the patent is valid, and unexpected results. *See Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

"A patent shall be presumed valid." 35 U.S.C. § 282. A party seeking to challenge the validity of a patent based on obviousness must demonstrate by clear and convincing evidence[2] that the invention described in the patent would have been obvious to a person of ordinary skill in the art at the time the invention was made. Importantly, in determining what would have been obvious to one of ordinary skill in the art, the use of hindsight is not permitted. *See KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 421 (2007) (cautioning the trier of fact against "the distortion caused by hindsight bias" and "arguments reliant upon ex post reasoning" in determining obviousness). In *KSR*, the Supreme Court rejected the rigid application of the principle that there should be an explicit "teaching, suggestion, or motivation" in the prior art, the nature of the problem, or the knowledge of a person having ordinary skill in the art, in order to find obviousness. *See id.* at 415.

[2] "Clear and convincing evidence is evidence that places in the fact finder an abiding conviction that the truth of [the] factual contentions are highly probable." *Alza Corp v. Andrx Pharms., LLC*, 607 F. Supp. 2d 614, 631 (D. Del. 2009) (internal quotations omitted) (quoting *Colorado v. New Mexico*, 467 U.S. 310, 316 (1984)).

The *KSR* Court acknowledged, however, the importance of identifying "'a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does' in an obviousness determination." *Takeda Chem. Indus. v. Alphapharm Pty. Ltd.*, 492 F.3d 1350, 1356–57 (Fed. Cir. 2007) (quoting *KSR*, 550 U.S. at 418).

"Obviousness does not require absolute predictability of success," but rather, requires "a reasonable expectation of success." *See Medichem, S.A. v. Rolado, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (quoting *In re O'Farrell*, 853 F.2d 894, 903–04 (Fed. Cir. 1988)). To this end, obviousness "cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). Moreover, while the Federal Circuit has noted that pharmaceuticals can be an "unpredictable art" to the extent that results may be unexpected, it also recognizes that, per *KSR*, evidence of a "finite number of identified, predictable solutions" or alternatives "might support an inference of obviousness." *See Eisai Co. Ltd. v. Dr. Reddy's Labs. Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008).

B. The Level of Ordinary Skill in the Art

A person of ordinary skill in the art with respect to the patents-in-suit would have: (1) a Ph.D. in chemistry, medicinal chemistry, pharmacology, or a related field;[3] or (2) a Ph.D. in organic chemistry, medicinal chemistry, pharmacology, biochemistry or a related discipline with two or more years of industrial experience in organic synthetic chemistry or drug formulation, and would collaborate with others having more biological experience in pertinent disciplines such as urology, medicine, and pharmacology.[4] Additional experience could substitute for the advanced degree. The

[3] The Plaintiffs' identification of a person of ordinary skill in the art is derived from Dr. Roush and Dr. Maag. (Tr. at 605:9–18 (Roush); Tr. at 531:20–532:6 (Maag).)

[4] Defendants' description of a personal of ordinary skill in the art is derived from Dr. Sloan. (Tr. at 301:3–23 (Sloan).)

court concludes that the parties' definitions of a person of ordinary skill in the art do not differ in a meaningful way.

C. The Scope and Content of the Prior Art and Differences Between the Claimed Subject Matter and the Prior Art

The Defendants argue a person of ordinary skill in the art would have found it obvious to synthesize fesoterodine as an improved overactive bladder treatment. The Defendants base their theory on the prior art molecule tolterodine and its metabolite, 5-HMT. To determine whether the Defendants have established a prima facie case of obviousness, the court must determine 1) "whether a chemist of ordinary skill would have selected the asserted prior art compounds as lead compounds, or starting points, for future development efforts"; and 2) whether the prior art would have supplied one of ordinary skill in the art with a reason or motivation to modify a lead compound to make the claimed compound with a reasonable expectation of success." *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1291–92 (Fed. Cir. 2012).

(1) 5-HMT as a Lead Compound

The Defendants argue a person of ordinary skill would have chosen 5-HMT as a lead compound for an improved overactive bladder treatment. As of the May 12, 1998 priority date, overactive bladder treatments included negative limitations such as urinary retention, dry mouth, and cardiac side effects. (D.I. 292 at 5.) The Defendants argue that a person of ordinary skill seeking to create an improved overactive bladder drug would only focus on antimuscarinic compounds. Antimuscarinic compounds block the neurotransmitter acetylcholine from binding to one of five types of muscarinic receptors in the body. Both parties agree that antimuscarinics were a popular treatment for overactive bladder at that time. (D.I. 292 at 5; D.I. 297 at 3.) Tolterodine and oxybutynin were the antimuscarinic compounds approved to treat overactive bladder in the United States. (Tr. at 760:7–18 (Serels).) Unlike oxybutynin, tolterodine and its metabolite 5-HMT were

selective for the urinary bladder over salivary glands, which reduced the adverse side effect of dry mouth. (Tr. at 213:7–19 (Mayersohn).) The Defendants claim that tolterodine's bladder selectivity would have motivated a person of ordinary skill to focus on developing 5-HMT.

The fatal flaw in the Defendants' lead compound theory is that their experts did not analyze the full field of overactive bladder treatments to determine what would qualify as a lead compound. The Plaintiffs' expert Dr. Maag testified that a person of ordinary skill would also consider other types of lead compounds, such as calcium channel antagonists, potassium channel antagonists, and alpha adrenoreceptor antagonists. (Tr. at 524:20–525:13, 528:7–17 (Maag)). Meanwhile, the Defendants' experts Dr. Mayersohn and Dr. Sloan narrowly considered tolterodine and 5-HMT and did not address other possibilities. (Tr. at 220:24–222:5 (Mayersohn); Tr. at 300:4–7 (Sloan).) Dr. Mayersohn's and Dr. Sloan's myopic approach to the field of overactive bladder treatments undermines their credibility. Based on Dr. Maag's testimony, the court concludes that a person of ordinary skill would have considered tolterodine and 5-HMT along with several other lead compounds.

(2) Modification of 5-HMT

After choosing tolterodine and 5-HMT as lead compounds, the Defendants argue that the prior art would have motivated a person of ordinary skill to modify 5-HMT. The prior art taught that tolterodine was metabolized differently across the patient population. Dr. Mayersohn and Dr. Sloan testified that this led to huge variations in bioavailability, and therefore, the effectiveness of the treatment. (Tr. at 163:21–191:12 (Mayersohn).) The Defendants argue that this shortcoming of tolterodine would motivate a person of ordinary skill to modify its metabolite, 5-HMT. In response, the Plaintiffs assert that the differential metabolism was clinically insignificant. (Tr. at 533:22–535:25 (Maag).) Dr. Maag discussed three prior art publications: the Brynne II reference (DTX

268), the Detrol® label (DTX 168), and the Nilvebrant article (DTX 57). These publications conclude that the pharmacokinetics of tolterodine do not produce significant differences in patient outcomes. (Tr. at 534:2–535:25 (Maag).) Dr. Mayersohn performed his own analysis of these publications and concluded that the studies were flawed. (Tr. at 191:13–192:13, 259:15–260:10, 205:3–208:8 (Mayersohn).)

Even if his conclusions are accurate, Dr. Mayersohn's post hoc analysis of the references' methodology does not persuade the court that a person of ordinary skill would have drawn the same conclusion during the relevant time period. Dr. Mayersohn did not point to any contemporary prior art contradicting the teaching of these references, and the references do not independently bear evidence of unreliability. The court is not convinced that a person of ordinary skill would have disregarded the Brynne II reference, the Detrol® label, and the Nilvebrant article. Therefore, the court concludes that the prior art does not suggest that tolterodine had a bioavailability problem.

The Defendants next argue that the prior art would motivate a person a skill to develop a new prodrug of 5-HMT. Tolterodine functions as a prodrug of 5-HMT. (Tr. at 321:1–14 (Sloan).) Based on 5-HMT's structure and its low lipophilicity, the Defendants argue that a person of ordinary skill would have understood that 5-HMT was too water soluble and would be poorly absorbed if administered without modification. (Tr. at 193:22–194:8 (Mayersohn), 330:7–332:2 (Sloan). Prodrug strategies were known options for modifying the lipophilicity and solubility of drug compounds. (Tr. at 194:9–19, 210:25–211:14 (Mayersohn); Tr. at 334:1–22 (Sloan); DTX283 at 1.) Therefore, the Defendants argue that a person of ordinary skill would have expected that creating a new prodrug of 5-HMT would yield a compound with similar, but improved properties over tolterodine and 5-HMT.

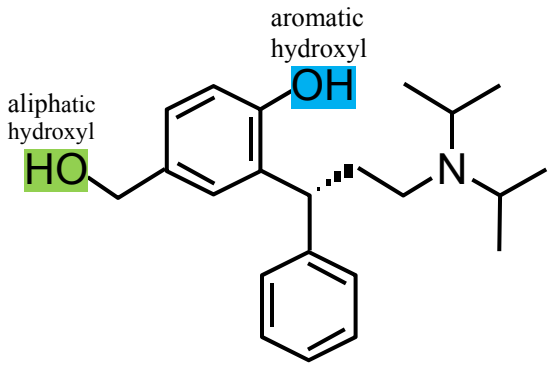
The Plaintiffs, however, offered unrefuted evidence that 5-HMT's oral absorption properties were, and still are, unknown. (Tr. at 532:9–22 (Maag); Tr. at 613:11–15 (Roush), Tr. at 235:17–236:6, 238:3–6 (Mayersohn)). Dr. Roush and Dr. Maag also testified that lipophilicity alone would not cause a person of ordinary skill to predict that 5-HMT would have an absorption problem. (Tr. at 612:19–613:10 (Roush), Tr. at 532:9–19 (Maag)). Even Dr. Sloan testified that although he expected 5-HMT to have worse absorption properties than tolterodine, he did not necessarily expect that to be a problem. (Tr. at 332:3–9, 324:3–5 (Sloan).)

The Plaintiffs also provided evidence that persons of ordinary skill viewed prodrug design as a complicated "last resort" approach due to: 1) higher potential for negative side effects due to multiple chemical moieties, (Tr. at 537:1–539:8 (Maag)); 2) difficulty balancing stability concerns, (Tr. at 553:7–16 (Maag); PTX-402 at 7; Tr. at 368:6–8, 373:24–374:2 (Sloan)); and 3) risk of premature metabolism, (Tr. at 538:12–23, 615:13–616:4; PTX-402 at 3). Dr. Maag testified that persons of ordinary skill would consider developing a prodrug only after satisfaction of the following conditions: 1) a well-known and valuable active molecule, but for a critical and unavoidable deficit; 2) a clearly defined and understood problem requiring use of a prodrug; 3) well-understood pharmacokinetics of the active molecule; and 4) a meaningful clinical advantage presented by the prodrug. (Tr. at 554:1–23 (Maag).) The Plaintiffs argue that the prior art presented 5-HMT as a poor choice for prodrug development because it did not meet any of the requirements outlined by Dr. Maag. (Tr. at 532:9–14 (Maag) (no known issue with 5-HMT); Tr. at 611:17–23 (Roush) (no clearly defined problem because no problem with oral absorption); Tr. at 236:4–9 (Mayersohn) (pharmacokinetics not well understood because oral absorption unknown); Tr. at 529:25–530:12 (Maag) (no meaningful clinical advantage because most patients already exposed to 5-HMT)).

Dr. Roush testified that a person of ordinary skill would first pursue non-prodrug approaches, such as performing structural modifications to create an analog of tolterodine, or experimenting with the formulation of 5-HMT. (Tr. at 607:15–611:1 (Roush).) The court agrees that the prior art would not have motivated a person of ordinary skill to create a prodrug of 5-HMT. The limited information about 5-HMT's properties, the risks associated with prodrug development, and the existence of more straightforward optimization techniques all indicate that a prodrug approach would not have been obvious.

(3) Chemical Structure of Fesoterodine

Even accepting the Defendants' supposition that it would have been obvious to create a new 5-HMT prodrug, the court does not find it would have been obvious to obtain the final chemical structure of fesoterodine. As illustrated below, 5-HMT contains two hydroxyl (-OH) groups that can be replaced with a prodrug group (promoiety): the aliphatic hydroxyl (left) and the aromatic hydroxyl (right). (PDX-1 at 20.) To obtain fesoterodine, the inventors replaced the aromatic hydroxyl with isobutyric ester. The Defendants argue that a limited amount of routine experimentation was required to arrive at this final result.



The Defendants argue that a person of ordinary skill would have chosen to develop an alkyl ester prodrug because esters were among the most commonly used promoieties. (DTX-279 at 2.) Dr. Sloan testified that a person of ordinary skill would have focused on small chain esters

containing two to six carbon atoms. (Tr. at 356:20–357:5 (Sloan).) Dr. Sloan testified that a person of ordinary skill would have focused on simplest modification first, replacing only one of the hydroxyl groups with an ester. (Tr. at 360:25–363:17 (Sloan).) Using the standard prodrug approach followed by the inventors, the Defendants argue that a person of ordinary skill would have obtained fesoterodine.

The Defendants' analysis contains several flaws. First, although the Defendants argue a person of ordinary skill would replace only one of the hydroxyl groups, the Plaintiffs note that 5-HMT contains four possible substitutions: single substitution at aliphatic hydroxyl, single substitution at aromatic hydroxyl, identical substitutions at both hydroxyls, or different substitutions at each hydroxyl group. (Tr. at 616:5–25 (Roush).) Second, Dr. Sloan initially opined in his initial expert report that a person of ordinary skill in the art would not have modified the aliphatic hydroxyl because doing so would making the resulting molecule too stable. (Tr. at 404:10–15 (Sloan).) But after attempting to modify the aliphatic hydroxyl, the inventors found that doing so made the molecule *unstable*. (Tr. at 49:12–49:6 (Meese).) After reviewing the inventors' results in this area, Dr. Sloan reversed his opinion. (Tr. at 405:13–19 (Sloan).) He admitted that the effect of modifying the aliphatic hydroxyl was not obvious to him at the time he submitted his initial report. (Tr. at 405:20–24 (Sloan).) This disclosure undermines Dr. Sloan's credibility regarding the obviousness of modifying 5-HMT to obtain the final structure of fesoterodine.

Third, the Defendants' experts did not provide any analysis of why a person of ordinary skill would not have considered numerous prodrug options outside of alkyl esters, such as phosphate esters, ethers, carbamates, or carbonates. (*See* Tr. at 614:2–615:12 (Roush).) Fourth, the Defendants provided no evidence specifically teaching towards isobutyryl promoiety, but argued that routine experimentation would yield that final result. Dr. Sloan listed at least four tests he would perform

to determine if a prodrug product was suitable. (Tr. at 360:7–20, 367:1-14 (Sloan).) The Plaintiffs note that even limiting potential promoieties to those presented by the Defendants—esters with two to six carbons—a person of ordinary skill in the art would have had over 7,500 options for modifying the 5-HMT molecule. (Tr. at 617:1–20 (Roush).) The sheer number of possible combinations contradicts the Defendants' assertion that it would have been obvious to replace the aromatic hydroxyl with the isobutyryl promoiety.

The inventors prepared 20 prodrug candidates and evaluated their conversion rates and absorption properties. (Tr. at 544:2–6, 547:24–548:16 (Maag).) Although the inventors followed a standard process to produce the 5-HMT prodrug, the Plaintiffs produced evidence that their experiments yielded unpredictable results. (Tr. at 546:2–20, 549:11–15 (Maag).) The court finds that the inventors' work involved a large amount of trial and error. Therefore, the court concludes Composition Patents are not invalid for obviousness.

(4) Salt Forms of Fesoterodine

The Defendants argue that it would have been obvious to make salt forms of fesoterodine as claimed in the'650 patent. Because fesoterodine is not prior art to the '650 patent, the Defendants must prove fesoterodine would have been obvious to invalidate its claims. The Defendants have failed to do so. Additionally, the preparation of salts can be a highly unpredictable exercise. (Tr. at 647:20–24, 678:9–16 (Chyall).) The inventor himself tested more than 70 salts, and initially only the hydrogen fumarate salt yielded the desired crystalline form. (Tr. at 58:14–59:8 (Meese).) Eventually, Dr. Meese discovered the hydrochloride hydrate salt of fesoterodine, which formed after the initial non-hydrate form was exposed to ambient moisture for some time. (Tr. at 63:4–64:16 (Meese).) The court concludes the asserted claims of the '650 patent are not obvious.

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In sum, the Defendants have failed to present a prima facie case that the asserted claims of the patents-in-suit are invalid as obvious.[5]

IV. CONCLUSION

For the reasons stated above, the court concludes that none of the asserted claims of the patents-in-suit are invalid due to obviousness.

Dated: April 20, 2016

UNITED STATES DISTRICT JUDGE

[5] Because the Defendants have failed to establish a prima facie case of obviousness, the court does not address the Plaintiffs' secondary considerations. *See Graham*, 383 U.S. at 17–18.